

Comments on Extrapolation of Cancer Response from High Dose to Low Dose

by Norton Nelson*

In making judgments as to the cancer risk from low level exposure to carcinogens it is generally necessary to base these judgments on high dose or high incidence data from laboratory or epidemiological studies. The biological considerations involved in making such extrapolations are discussed, as well as some of the mathematical procedures. The difficulties presented by moving from species to species, or from differently acting carcinogenic agents is considered.

Prediction from high cancer incidence in humans or laboratory animals to the lower levels possibly associated with community air pollution is difficult. At the present time, it seems that projections from human epidemiological data are more reliable, uncertain though they may be, than are projections from laboratory animals.

The art of quantitative evaluation of carcinogenicity in laboratory animals has progressed immensely in the past twenty years. It seems reasonably reliable in simple situations, but uncertain in more complex circumstances.

If one makes the assumption that intrinsic tissue sensitivity is reasonably uniform from species to species (there are exceptions), dosage can be computed on a rational basis moving between species, and from higher and lower doses, especially where the tumors are produced in the exposed tissue by direct-acting carcinogens.

With high dose, direct-acting agents, e.g., ionizing radiation or alkylating chemicals, confidence in quantitative inferences is highest. Thus in the direct production of skin cancer from ionizing radiation (1), or from inhaled alkylating agents, e.g., bis(chloromethyl)ether (2), one is dealing with direct dosage of the responsive tissue. Also, promoting or cocarcinogenic factors are probably of less importance in the high dose-response range. On the other hand, it is perfectly clear that even with ionizing radiation, coacting factors can be of decisive

importance. Thus, doses of ionizing radiation producing a significant response of breast cancer in rats (3), or leukemia in AKR mice (4), are considerably lower than those producing epithelial cancer in skin. Are viral or hormonal factors responsible for the greater radiation sensitivity? It seems very possible that they are. It is also clear that cigarette smoking is a powerful synergistic factor in the production of lung cancer in uranium miners (5).

When one moves from direct-acting chemical agents to those that require activation, such as aromatic amines (β -naphthylamine and benzidine) or the hydrocarbons (benzo[a]pyrene), the situation becomes much more uncertain.

These additional variables enter the equation when there are species differences in activating and inactivating enzymes. We know very well that these species variations can in some cases be substantial. Thus, β -naphthylamine produces bladder cancer in the dog and in hamsters to a lesser extent, while other species are essentially nonresponsive to bladder cancer from this agent. Analysis of the situation, where the activation of the carcinogen occurs in the tissue or cell where the tumors are produced, e.g., skin painting with benzo[a]pyrene, is simpler than where the activation occurs in one organ and the tumors are produced in another. In the latter case, confidence in the projections must necessarily be additionally weakened.

It seems highly probable that in most real-life human cancer, modulating factors, cocarcinogens, and promoting agents, play very important roles. Certainly there is every reason to believe that this is true of lung cancer.

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Our own work has shown that the lung cancer yield from benzo[a]pyrene goes up with local injury and procedures which enhance persistence (pellet or thread implant), and with irritants such as sulfur dioxide and nitrogen dioxide (6). In the case of air pollution there is reason to believe that smoking intensifies the response to air pollution (7).

The use of laboratory animal models for estimates of response which are meaningful for humans is thus, no doubt useful in some of the simpler situations but becomes progressively less reliable as the steps involved increase in complexity, i.e., one species to another; agents requiring activation; activation in one organ, tumors in another; and major influence of stimulatory or inhibitory coacting enzymes or agents. Accordingly, laboratory studies are of great utility for yes or no answers, for direct comparison of agents within the same family of compounds, for comparison of the influence of selected stimulatory or inhibitory factors on the same agent, but inspire less confidence as the situation grows more complex.

The forms of the curves relating cancer response to dose have received much attention and one can find in the literature examples to support almost any postulated pattern. Breast cancer in the rat from ionizing radiation starts well above zero and is substantially linear (3); lung cancer in the rat, with ionizing radiation, probably approximates linearity at low doses but is concave upward in the higher dose ranges (8). A similar pattern is found with chemical carcinogens in the rat with regard to lung cancer (8). Leukemia arising from radiation of patients with spondylitis shows concavity upward over a broad dose range but essential linearity at low dose spans (9).

Such curves exhibit, at first glance, a quasi-threshold; closer inspection usually shows them to be lines with lower slope starting from the origin and then moving exponentially up. There is no reason to believe that carcinogens which show thresholds will not eventually be identified. It seems logical to assume that, where detoxifying processes (enzymatic or nonenzymatic) are functioning, very low levels of some agents will be inactivated before they reach the biochemical element of the cell (DNA) required for the production of malignancy. However, at this time I am unaware of any well documented demonstration of such a threshold.

Numerous dose-response models varying sophistication have been devised. This is a field now receiving far more attention than it has in the past. Some of these models are extrapolation systems, which, by the incorporation of safety factors, aim at conservatism. These cannot be regarded as an un-

biased, or "most plausible" analysis of response to dose. The Mantel/Bryan procedure is an example of this which, by choice of slope, automatically incorporates a safety factor (10). A procedure which attempts a "most plausible" estimate has been described by Albert and Altshuler (11). This incorporates a time-to-tumor-occurrence component, as well as incidence or frequency of tumors. Any relevant model must take into account time to occurrence, since there is clear evidence that with higher dose, tumors occur earlier than with lower doses. The practical application of such models at this time is very restricted, since the basic data are rarely available. Albert and Altshuler, however, have shown that the model fits a number of patterns of cancer occurrence in animals exposed to chemical carcinogens and ionizing radiation, and have also shown that it fits the lung cancer-cigarette smoking relationship in humans.

In summary, it appears that at the present time the most confident estimation of the quantitative impact of air pollution on human cancer will come from epidemiological data which in some instances will be reinforced by laboratory data on animals.

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